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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,521	08/27/2001	Jian-Yun Dong	22488-710	7109

21971 7590 02/18/2004

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant 02/09/04 Cy

Office Action Summary	Application No.	Applicant(s)	
	09/600,521	DONG ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *d3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47 and 58-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47 and 58-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group X in response filed on December 01, 2003 is acknowledged. Applicant has canceled claims 1-46, 48-57 and 74-112. Claims under consideration are claims 47, 58-73 (i.e. Group X).

Specification

The disclosure is objected to because of the following informalities: On p. 4, ll. 8 and 12, and on p. 25, l. 14, the capital letter "A" appears out of place and confers no meaning; on p. 6, l. 2, growth is misspelled: "groth". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 47, 58-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claim 47 is drawn to a method of inducing death in cells expressing an apoptosis-mediating receptor, by introducing an expression vector into a group of cells that may or may not express the apoptosis-mediating receptor, where the vector expresses an apoptosis-signaling ligand.

The claim is unclear and indefinite because it recites that the receptor, through "interaction" with the ligand, induces cell death. The term "interaction" is not sufficiently defined, so that the claims' metes and bounds are indefinite. For example, it is known in the art that FasL (ligand) upon *binding* Fas (receptor) causes trimerization of the receptor, an essential requirement for apoptopic signaling. (*See generally*, Pinkoski and Green. Cell Death and Differentiation, 6:1174-81, at 1174, col. 2 (1999)). If applicant is claiming a ligand-receptor-interaction exclusive of *binding*, it is unclear from the claim as well as the disclosure, what is the nature of this interaction. The specification only indicates that, "the interaction does not have to be binding per se, but includes any cellular reaction which results from any interaction of the Fas and the Fas ligand." (Spec. p. 23, ll. 1-5). Furthermore, the disclosure does not actually characterize or measure the ligand-receptor interaction directly, but rather, measures apoptosis in ligand-expressing (transformed cells) or adjacent cells (not transformed; bystander effect).

Therefore, there is no clarification as to what "interaction" means. This is not merely a claim's breadth issue, because while the term "interaction" is broad, it confers an ambiguous and indefinite meaning. For example, an expression vector could be used to express a ligand which itself elicits antibodies to be produced, which are the actual effector molecules binding the receptor, thus signaling apoptosis. Thus while "binding" would be a term of clarity and precision, one of ordinary skill in the art would not be able to predict the claims' metes and bounds, where the ambiguous and indefinite term "interaction" is used.

In addition, claim 47 is unclear and ambiguous, because it is drawn to a process involving an apoptosis-mediating receptor and an apoptosis-mediating ligand. It is unclear if applicant intends the invention to read on any ligand and any receptor, or rather what appears to be

intended, the interaction of any receptor and its specific cognate ligand. It would be remedial to insert the term "cognate" or "specific" to confer the proper relationship.

2. **Claims 47, 58-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* use, FasL-Fas mediated cell death and the vector rAD/FasL-GFP$_{TETd}$, does not reasonably provide enablement for *in vivo* use, cell death via expressing any ligand in any ligand-receptor-mediated apoptosis and expression of FasL using any expression vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.**

The invention is drawn to a process of gene therapy where cells are transfected with an adenoviral vector expressing apoptosis-mediating ligand, where a Tet-responsive promoter regulates expression.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims: The scope/breadth of the claims are broad, where the claims are drawn to a process of inducing cell death involving transfection of any cell expressing any apoptosis-mediating receptor, with any expression vector (more particularly plasmid or viral vectors), which encode any apoptosis-mediating ligand. Thus, the claims encompass in vivo embodiments directed to therapy.

Nature of the invention: The invention is primarily based on a process involving gene therapy, where a replication-deficient adenoviral vector encoding a murine Fas Ligand is used to transfect cells, with subsequent regulated expression (i.e. down regulation via the Tet-responsive regulatory element) of the ligand in cells that may express the Fas receptor. The contemplated use is *in vivo*, for eradication of cancerous cells or tumors in a subject (e.g. human subjects).

State of the art: The invention is directed to gene therapy and specifically to targeting tumor cells expressing Fas receptor using an adenoviral expression construct encoding FasL. With regard to gene therapy, the state of art is also poorly developed. "...there is still no conclusive evidence that gene-therapy protocol has been successful in the treatment of a human disease." (*See*, Anderson, Nature, 392: 25-30, at 25 (1998)).

Furthermore, with regard to use of adenoviral vectors in tumor targeting, there are significant hurdles that need to be overcome: unwanted infection of non-target cells, evasion of neutralization by anti-adenoviral antibodies, viral interaction with blood cells, immune parameters affecting efficacy and toxicity and viral bio-distribution. (*See*, Green and Seymour. Cancer Gene Therapy; 9:1036-42, pp. 1039-40 (2002)).

In addition, while the Fas and FasL mediated pathway for apoptosis is well characterized, studies conducted with regard to targeted inducement of cell death have been exclusively *in vitro*

or in immunocompromised mice. (e.g., Arai et al. *Gene transfer of Fas ligand induces tumor regression in vivo*. Proc. Natl. Acad. Sci. 94:13862-7 (Dec. 1997)); (showing apoptosis of colon carcinoma tumors implanted into flanks of nude mice, where tumors were injected with adenoviral vectors expressing FasL). More importantly, clinical studies studying the therapeutic effect of FasL in killing cancer cells were disappointing due to "severe toxicity observed in preclinical studies". (*See*, Rossi and Gaidano. Haematologica/J. Hematology, 88(2):212-18, at 217 (2003)).

Another attendant problem with FasL expression is hepatotoxicity, as there is substantial Fas receptor expression in liver cells. Even with regulatable FasL expression, *in vitro* results do not necessarily translate into *in vivo* use. For example, having base line FasL expression or "leaky" expression can result in unintended toxic effects, making practice of invention impossible. Moreover, Fas receptors are widely expressed by many normal cells in the body, therefore extending the potential for toxicity to different tissue/organs. In sum, the state of art, viz., *in vivo* expression of a ligand in a ligand-receptor mediated (e.g. Fas-FasL) apoptosis, is still developing with many substantial concerns and question yet to be resolved.

Unpredictability of the art: With regard to the invention reading on gene therapy, there is a great deal of unpredictability. Gene therapy is still a highly unpredictable art within biology and medicine. For example, nucleic acids encoding therapeutic products may be erroneously inserted, thus disrupting a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, E., Nature, 421: 678 (2003)) (citing occurrence of leukemia due to insertion nucleic acids used in gene therapy into a particular stretch of DNA); (*See also*, Juengst, ET. BMJ,

326:1410-11(2003)) (indicating that gene transfer often has multiple and unpredictable effects on cells).

More specifically, with regard to adenoviral vectors for targeting tumor targeting *in vivo*, there is a substantial risk of vector immunogenicity, such as localized inflammation that can occur at the site of gene transfer due to T- or B-Cell mediated targeting of transduced cells. In addition, both neutralizing (which would hinder expression of the therapeutic gene; i.e. FasL) and non-neutralizing anti-adenovirus antibodies are capable of activating complement. (*See supra*, Green and Seymour, at 1039, col. 2, ¶ 2). Furthermore, if viral vectors enter the systemic system, whether expressing FasL or not, they can be delivered to other cells exacerbating the immune response. Moreover, FasL expression could have deleterious effects on normal cells expressing Fas receptor, whether FasL is expressed by transfected cancer cells or transfected non-target cells.

With regard to Fas and FasL mediated apoptosis in gene therapy. As the state of the art is poorly developed, it would follow that there is a great deal of unpredictability as to whether expression of FasL *in vivo* would result in cell death in cancer cells expressing Fas receptor. For example, even if viral transfection can avoid the problems with adenoviral vector introduction *in vivo*, cancer cells that do not express Fas receptor would actually proliferate. In addition, expressing FasL may have unintended deleterious effects on the bodie's anti-cancer defense.

One such effect is tumor immune privilege; this occurs where intra-tumoral lymphocytes, such as natural killer cells (the main anti-tumor effector cells, which highly express Fas receptor) are actually "attacked" by cancer cells that express FasL. (*See*, O'Connell et al. Nature Med.,

5(3):267-8, at 267 (1999)). In sum, it must be deemed that there is a great deal of unpredictability that is attendant with practicing the claimed invention.

With regard to expression vectors, while the claims are drawn to any vector, more specifically plasmid and viral vectors, one of ordinary skill in the art would recognize that even within the broad narrower group of viral vectors, there would be concurrent problems of transfection efficiency, expression control, non-target integration, gene disruption, immune response neutralization or toxisosis. Each vector could have a differential set of factors that the artisan would need to address in order to practice the invention. The salient point being, that even if applicant had addressed the variable factors with regard to rAD/FasL-GFP_{TETd}, this would not necessarily translate into enablement for all vectors.

Amount of guidance provided/working examples: The specification provides a single example replication-deficient adenoviral vector expressing a murine FasL (i.e. rAD/FasL-GFP_{TETd}) that results in apoptosis of cells expressing the Fas receptor, *in vitro* cell culture and *in vivo* in immunocompromised mice, where breast cancer and prostate cancer cell lines are deposited in nude mice. The disclosure also provides prophetic, guidance on how to make and use an *up-regulated* version of the rAD/FasL-GFP_{TET} vector.

In addition the disclosure indicates experiments involving immunocompetent dogs were conducted, but there are no results set forth. (Spec. pp. 39-40, "Toxicology...beagles"). Therefore, there are no *in vivo* examples and there is no guidance given in this regard, where the animal model is immunocompetent. Moreover, if such data is available it would not obviate the obstacles attendant to immunotoxicity and immunoneutralization that would be attendant to human subjects and transfection of adenoviral vectors, as such factors would be exclusive of

obstacles and unpredictability related to FasL expression in target and non-target cells. No other combinations of receptor/ligand are taught in the instant specification.

Amount of experimentation required: The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successfully practicing the invention, the level of unpredictability in the art and lack of working examples *in vivo*, as outlined above, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue, unpredictable nature in order to attempt to practice the claimed invention commensurate with claims' scope.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. **Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Larregina et al. (Gene Therapy, Jan. 1998, 5:563-568; hereinafter Larregina).**

The claim is drawn to a method of inducing cell death in cells expressing an apoptosis mediating receptor (e.g. Fas), through introducing into the cells an expression vector expressing an apoptosis-signaling ligand (e.g. FasL), where the vector is under control of a conditional promoter.

Larregina teaches introducing an adenoviral expression vector, expressing the FasL ligand, which upon binding its receptor, Fas, mediates cell death, where the expression is controlled by the constitutive promoter CMV. (e.g. Abstract, p. 564, col. 2). However, Larregina teaches, that to preclude unwanted cell death (i.e. regulated FasL expression), the vector should be modified to express FasL under control of tissue specific and /or inducible promoter elements. (e.g. Abstract, p. 566, col. 2).

The ordinary skilled artisan seeking to develop a method of expressing FasL under a regulated or tissue-specific fashion would be motivated to modify the vector taught in Larregina to contain a conditional promoter element (as the reference itself expresses). It would have been obvious for the ordinary skilled artisan to so modify the adenoviral vector so as to regulate FasL expression, thereby regulating apoptosis of the cells expressing the Fas receptor. Given the teachings of the cited reference and the level of skill of the ordinary skilled artisan at the time of applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

4. **Claims 47 and 58-73 Larregina et al. (Gene Therapy, Jan. 1998, 5:563-568). and further in view of Arai et al. (Proc. Natl. Acad. Sci. Dec. 1997, 94:13862-7; hereinafter Arai)**

The claims are drawn to a method of inducing death in a group of cells that express an apoptosis receptor (e.g. Fas), by introducing an expression vector comprising a nucleotide sequence encoding an apoptosis-signaling ligand, where expression is activated through a suitable conditional promoter, so that the ligand so produced mediates apoptosis through interaction with the receptor. The group of cells can be contained in a solid tumor and selected from different tissue/organ (e.g. breast, colon, stomach). The expression vector can be plasmid, viral and the conditional promoter can be tissue-specific (e.g. prostate-specific promoters) or inducible (e.g. Tet-responsive promoter, or steroid).

Larregina teaches using tissue-specific and/or inducible promoter elements to control FasL expression in cells that express the Fas receptor. (e.g., Abstract, p. 566, col. 2, ¶ 3). Although Larregina teaches regulation of expression for the purposes of production and purification of FasL-expressing adenoviral vectors, the reference teaches that the FasL-Fas mediated apoptosis can be regulated so as to precluded unwanted cell death.

Larregina does not teach introducing the expression vector into a group of cells that are tumor cells or different types of tumor cells.

Arai teaches apoptosis of colon carcinoma tumors implanted into flanks of nude mice, where tumors were injected with adenoviral vectors expressing FasL and where the cancerous cells express the receptor Fas, but where expression is under regulation of the constitutive promoter (e.g. CMV). (e.g. Abstract, p. 13863, col. 2, under Results). Aria teaches using nude

mice (i.e. immunocompromised) to implant tumors, into which the adenoviral vector is injected and expresses FasL, which mediates apoptosis through binding with the Fas receptor. (e.g., pp. 13863, col. 1, ¶ 5). That different tumors from different cells would be susceptible to the receptor-ligand mediated apoptosis is of little moment, because the Fas-FasL mediated apoptosis is well characterized. Thus, tumor cells expressing the receptor would be equivalents for the purposes of the invention. Put another way, breast tumor cells, prostate tumor cells and colon tumor cells would be part of an equivalent group of cells, viz., Fas-FasL mediated apoptosis.

The ordinary skilled artisan seeking to develop an *in vitro* process for regulating expression of FasL in a transfected group of cells would be motivated to modify the vector taught by Aria with the conditional/tissue-specific vector taught by Larregina. Conditional/tissue-specific promoters were well known at the time of applicant's invention (e.g. Miller and Whelan, Human Gene Therapy, May, 1997, 8:803-815; e.g. Table 1, outlining may control sequences; p. 807, col. 2, citing PSA promoter; p. 810, Fig. 1, citing Tet-responsive element). Because of what is taught by the references cited, it would have been obvious for the ordinary skilled artisan modify the vector with the significant improvement of regulated expression of a ligand, in a ligand-receptor mediated cell death mechanism. Given the teachings of the cited references and level of skill of the ordinary skilled artisan at the time of applicant's invention, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GERRY LEFFERS
PRIMARY EXAMINER